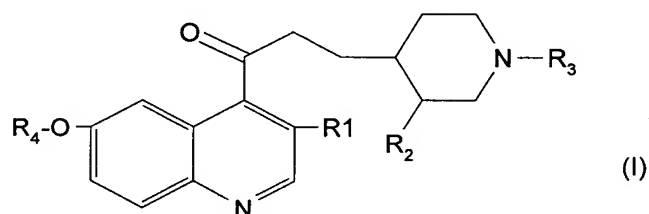


QUINOLYLPROPYLPYPERIDINE DERIVATIVES, INTERMEDIATES AND
COMPOSITIONS CONTAINING THEM, AND PREPARATION THEREFOR

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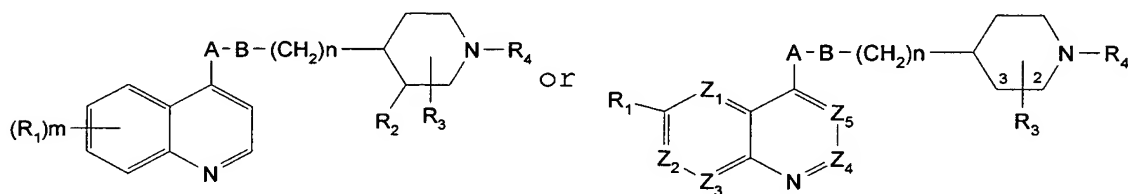
This application claims the benefit of priority of French Patent Application No. 02/11,212, filed September 11, 2002.

10 The present invention relates to quinolypropyl-piperidine derivatives of general formula (I):



15 which are active as antimicrobials. The invention also relates to intermediates, compositions containing them, and to their preparation.

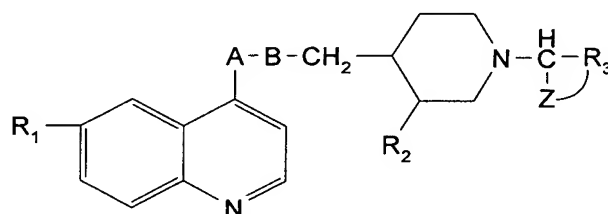
20 In Patent Applications WO 99/37635 and WO 00/43383, there have been described antimicrobial quinolypropyl-piperidine derivatives of general formula:



25 in which the radical R₁ is in particular (C1-6)alkoxy, R₂ is hydrogen, R₃ is at the 2- or 3-position and represents (C1-6)alkyl which may be optionally substituted with 1 to 3 substituents chosen from thiol, halogen, alkylthio, trifluoromethyl, carboxyl, alkyl-

oxycarbonyl, alkylcarbonyl, alkenyloxycarbonyl, alkenylcarbonyl, hydroxyl optionally substituted with alkyl, and the like, R_4 is a group $-CH_2-R_5$ for which R_5 is selected from alkyl, hydroxyalkyl, alkenyl, alkynyl, tetrahydrofuryl, phenylalkyl which is optionally substituted, phenylalkenyl which is optionally substituted, heteroarylalkyl which is optionally substituted, heteroaryl which is optionally substituted, and the like, n is 0 to 2, m is 1 or 2 and A and B are in particular oxygen, sulfur, sulfinyl, sulfonyl, NR_{11} , CR_6R_7 for which R_6 and R_7 represent H, thiol, alkylthio, halo, trifluoromethyl, alkenyl, alkenylcarbonyl, hydroxyl, amino, and Z_1 to Z_5 are N or CR_{1a} , and the like.

In European Patent Application EP 30044, there have been described quinoline derivatives which are useful as cardiovascular agents and which correspond to the general formula:



in which R_1 is H, OH or in particular alkyloxy, $A-B$ is $-CH_2-CH_2-$, $-CHOH-CH_2-$, $-CH_2-CHOH-$, $-CH_2-CO-$ or $-CO-CH_2-$, R_2 is ethyl or vinyl, R_3 is in particular alkyl, hydroxyalkyl, cycloalkyl, hydroxyl, alkenyl, alkynyl, tetrahydrofuryl, phenylalkyl, diphenylalkyl which is optionally substituted, phenylalkenyl which is optionally substituted, benzoyl or benzoylalkyl which is optionally substituted, heteroaryl or heteroarylalkyl which is optionally substituted and Z is H or alkyl or forms with R_3 a cycloalkyl radical.

It has now been found, and this is what constitutes the subject of the present invention, that the products of

general formula (I) for which:

R₁ is a hydrogen or fluorine atom,

5 R₂ represents a carboxyl, carboxymethyl or hydroxymethyl radical,

R₃ represents an alkyl (1 to 6 carbon atoms) radical substituted with a phenylthio radical which may itself
10 carry 1 to 4 substituents chosen from the group consisting of halogen, hydroxyl, alkyl, alkyloxy, trifluoromethyl, trifluoromethoxy, carboxyl, alkyloxy-carbonyl, cyano and amino, with a cycloalkylthio radical in which the cyclic portion contains 3 to 7
15 members, which may itself carry one or more substituents chosen from halogen and trifluoromethyl, or with a 5- to 6-membered heteroarylthio radical comprising 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur which may itself carry one or more
20 substituents chosen from the group consisting of halogen, hydroxyl, alkyl, alkyloxy, trifluoromethyl, trifluoromethoxy, carboxyl, alkyloxy-carbonyl, cyano and amino or R₃ represents a propargyl radical substituted with a phenyl radical which may itself carry 1 to 4
25 substituents chosen from the group consisting of halogen, hydroxyl, alkyl, alkyloxy, trifluoromethyl, trifluoromethoxy, carboxyl, alkyloxy-carbonyl, cyano and amino, or substituted with a 3- to 7-membered cycloalkyl radical which may itself carry one or more
30 substituents chosen from halogen and trifluoromethyl, or substituted with a 5- to 6-membered heteroaryl radical comprising 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur and which may itself carry one or more substituents chosen from the group
35 consisting of halogen, hydroxyl, alkyl, alkyloxy, trifluoromethyl, trifluoromethoxy, carboxyl, alkyloxy-carbonyl, cyano and amino, and

R₄ represents an alkyl radical containing 1 to 6 carbon

atoms, an alkenyl-CH₂- or alkynyl-CH₂- radical in which the alkenyl or alkynyl portions contain 2 to 6 carbon atoms, or a cycloalkyl or cycloalkylalkyl radical in which the cycloalkyl portion contains 3 to 8 carbon atoms,

in their isomeric, enantiomeric and diastereoisomeric forms, separate or as mixtures, and also their salts, are potent antibacterial agents.

10

It is understood that the alkyl radicals and portions are in the form of a straight or branched chain and contain (unless otherwise stated) 1 to 4 carbon atoms, and that when R₃ carries a halogen substituent, the latter may be chosen from fluorine, chlorine, bromine and iodine, fluorine being preferred.

15

In the above general formula, when R₃ carries a heteroaryl substituent, the latter may be chosen, without limitation, from thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrazinyl and pyrimidinyl.

20

A subject of the invention is in particular the derivatives of general formula (I) as defined above, in which R₄ represents an alkyl radical containing from 1 to 6 carbon atoms, in particular methyl, those in which R₂ represents a carboxyl radical and those in which R₃ represents an alkyl radical, in particular ethyl, substituted with a phenylthio, cycloalkylthio or heteroarylthio radical optionally substituted as defined above, more particularly those in which R₃ represents an ethyl radical substituted with a thienylthio radical or a phenylthio radical substituted with halogen, in particular fluorine, or with trifluoromethyl, cyclohexylthio or cyclopentylthio, and those with the following names:

30

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1-(2-cyclohexylsulfanylethyl)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]piperidine-3-carboxylic acid,

5 4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxo-propyl]-
1-[3-(2,3,5-trifluorophenyl)prop-2-ynyl]piperidine-
3-carboxylic acid,

4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-
10 1-[2-(2,5-difluorophenylsulfanyl)ethyl]piperidine-
3-carboxylic acid,

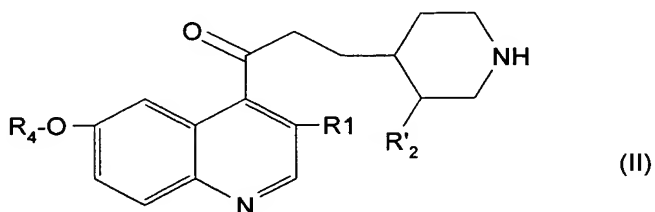
4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-
1-[2-(2,5-difluorophenylsulfanyl)ethyl]piperidine-
15 3-acetic acid,

4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-
1-[2-(2-thienylsulfanyl)ethyl]piperidine-3-carboxylic
acid,

20 4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-
1-[3-(2,3,5-trifluorophenyl)prop-2-ynyl]piperidine-
3-carboxylic acid,

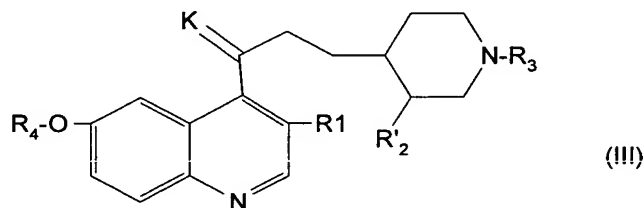
25 in their various isomeric forms, separate or as mixtures,
as well as their salts.

According to the invention, the products of general
formula (I) may be obtained according to process A by
30 condensing the R₃ chain with the quinolylpropyl-
piperidine derivative of general formula (II):



35 in which the ketone functional group is, where

appropriate, intermediately protected, R_1 and R_4 are defined as above and R'_2 represents a protected carboxyl or carboxymethyl radical, to obtain a quinolyl-propylpiperidine derivative of general formula (III):



for which R_1 , R'_2 , R_3 and R_4 are as defined above and K represents an oxygen atom or a ketone-protecting group, then conversion of R'_2 to a carboxyl or carboxymethyl radical, and/or, where appropriate, reduction of the carboxyl radical thus obtained or of the protected carboxyl radical which may be represented by R'_2 to a hydroxymethyl radical and, optionally, conversion thereof to a carboxymethyl radical according to usual methods, then, where appropriate, separation of the isomers, removal of the acid-protecting radical, removal of the ketone-protecting radical, and/or conversion of the product obtained to a salt.

20

The condensation of the chain R_3 with piperidine is advantageously carried out by the action of a derivative of general formula:

25



(IV)

in which R_3 is as defined above and X represents a halogen atom, a methylsulfonyloxy radical, a trifluoromethylsulfonyloxy or p-toluenesulfonyloxy radical, the procedure being carried out in an anhydrous, preferably inert (nitrogen or argon for example) medium, in an organic solvent such as an amide (dimethylformamide for example), a ketone (acetone for example) or a nitrile (acetonitrile for example) in the presence of a base such as a nitrogen-containing organic base (for example

30

35

triethylamine) or an inorganic base (alkali metal carbonate:potassium carbonate for example) at a temperature of between 20°C and the reflux temperature of the solvent.

5

Preferably, a derivative for which X is a bromine or iodine atom is caused to react.

10

Derivatives of formula (IV) are described or can be prepared as described, for example, in applications WO 200125227 and WO 200240474.

15

When R₃ represents propargyl substituted with phenyl, cycloalkyl or heteroaryl, it may also be preferable to condense a propargyl halide, and then to substitute the chain with a phenyl, cycloalkyl or heteroaryl radical. In this alternative case, the condensation of the propargyl chain is carried out by means of propargyl bromide, under the conditions set out above in the presence, where appropriate, of an alkali metal iodide such as for example potassium or sodium iodide.

20

When substitution with a phenyl or heteroaryl radical is involved, the reaction is carried out by the action of a halide derived from the cyclic radical to be substituted, in the presence of triethylamine, in anhydrous medium, optionally with no solvent or in a solvent such as an amide (dimethylformamide for example) or a nitrile (acetonitrile for example) and in the presence of a palladium salt such as for example tetrakis(triphenylphosphine)palladium and copper(I) iodide, at a temperature of between 20°C and the reflux temperature of the solvent.

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When substitution with a cycloalkyl group is involved, the reaction is carried out, after protection, in the form of an acetal which may or may not be cyclic, of the ketone functional group in the alpha-position of the quinoline, by the action of an organolithium

compound such as n-butyllithium or tert-butyllithium on the propargyl derivative obtained above, in anhydrous medium in an ether such as for example tetrahydrofuran at a temperature of between -78 and 0°C, followed by
5 the action of a cycloalkanone followed by the deoxygenation of the intermediate alcohol and, finally, by the deprotection of the ketone functional group according to conventional methods.

10 It is understood that when the alkyl radicals represented by R_3 carry carboxyl or amino substituents, the latter are protected beforehand and then released after the reaction. The procedure is carried out according to customary methods which do not adversely affect the
15 rest of the molecule, in particular according to the methods described by T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis (2nd ed.), A. Wiley - Interscience Publication (1991), or by Mc Omie, Protective Groups in Organic Chemistry, Plenum
20 Press (1973).

The protected carboxyl or carboxymethyl radical represented by R'_2 may be chosen from the easily hydrolyzable esters. By way of example, there may be
25 mentioned methyl, benzyl or tert-butyl esters, or allyl or phenylpropyl esters. Where appropriate, the carboxyl radical is protected simultaneously with the reaction. In this case, the product of general formula (II) used carries a radical R'_2 which is a carboxyl or carboxy-
30 methyl radical.

The removal, where appropriate, of the acid-protecting radical in order to obtain a quinolypropylpiperidine derivative for which R_2 is a carboxyl or carboxymethyl
35 radical, is carried out according to usual methods, in particular by acid hydrolysis or saponification of the ester R'_2 . The sodium hydroxide is in particular reacted in aqueous-organic medium, for example in an alcohol such as methanol or an ether such as dioxane,

at a temperature of between 20°C and the reflux temperature of the reaction mixture. Hydrolysis in aqueous hydrochloric acid at a temperature of between 20 and 100°C can also be used.

5

According to the invention, the derivative of general formula (I) for which R₂ is hydroxymethyl can be prepared by the action of a suitable reducing agent on a derivative for which R'₂ is carboxyl or protected carboxyl. Before carrying out such a reduction reaction, the ketone functional group in the alpha-position of the quinoline is first protected by a suitable protecting group which sustains the reduction conditions, as described further below. Also according to the invention, the derivative of general formula (I) for which R₂ is carboxymethyl can be prepared from the derivative for which R'₂ is hydroxymethyl, obtained as described above, by the action thereon of a halogenating or tosylating agent, then of a cyanating agent and, finally, hydrolysis of the nitrile.

More specifically, the reduction of the carboxyl can be carried out according to usual methods which do not alter the rest of the molecule, in particular by the action of a hydride (lithiumaluminum hydride or diisobutyl aluminum hydride for example) in a solvent such as an ether (tetrahydrofuran for example) at a temperature of between 20 and 60°C. The ketone functional group in the alpha-position of the quinoline is intermediately protected and then deprotected according to conventional methods known to those skilled in the art, in particular via an acetal which may or may not be cyclic.

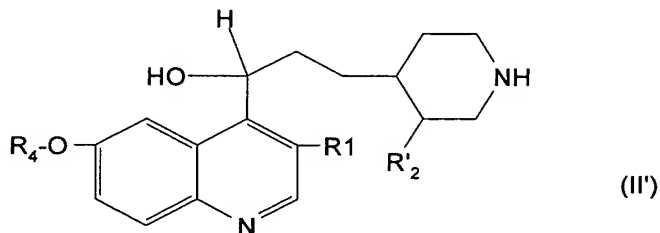
The reduction of the free acid can be carried out according to methods also known to those skilled in the art, for example by hydrogenation in the presence of a rhodium-based or ruthenium-based catalyst, by the action of sodium hydroboride in the presence of a Lewis

acid or of lithiumaluminum hydride in ether. Preferably, the ketone functional group is, in this case, also intermediately protected.

5 The conversion of the hydroxymethyl radical in the 3-position of the piperidine to a carboxymethyl radical is carried out according to usual methods which do not alter the rest of the molecule, in particular by the action of a halogenating agent, such as, for example,
10 thionyl chloride or phosphorus trichloride or phosphorus tribromide, or of a tosylating agent, and then of an alkali metal cyanide, for example potassium cyanide or sodium cyanide, to prepare the corresponding cyanomethyl derivative, followed by hydrolysis of the
15 nitrile.

The halogenation can be carried out in a chlorinated solvent (dichloromethane or chloroform for example) at a suitable reaction temperature, which can be
20 subambient, ambient or superambient. For example, a temperature of between 0°C and the reflux temperature of the solvent may be employed.

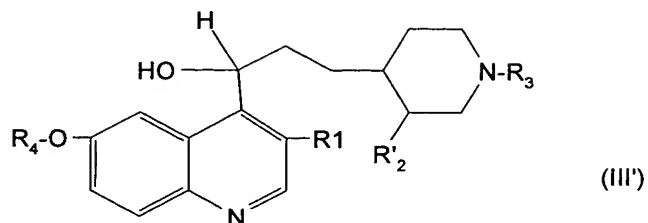
According to the invention, the products of general
25 formula (I) may also be obtained according to process B, by condensing the R₃ chain with the quinolylpropylpiperidine derivative (II') of general formula:



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in which R₁ and R₄ are as defined above and R'₂ represents a protected carboxyl or carboxymethyl radical, to obtain a quinolylpropylpiperidine deriva-

tive of general formula (III'):



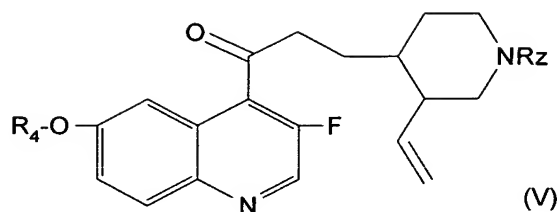
5 in which R_1 , R'_2 and R_4 are as defined above and R_3 is as defined previously, then oxidation of the alcohol functional group in the alpha-position of the quinoline to a ketone, to obtain a derivative of formula (III) as defined above, in which R_1 , R'_2 and R_4 are as defined above
 10 and K represents an oxygen atom, and continuation of the synthesis as described above.

The condensation of the R_3 chain with the piperidine is carried out under the same conditions as those described
 15 in method A.

The oxidation of the alcohol functional group to a ketone is carried out by conventional methods which do not alter the rest of the molecule, for example by
 20 oxidation according to D. Swern, J.O.C., 44, 41-48 (1979), in particular in the presence of oxalyl chloride and of dimethyl sulfoxide, where appropriate in a solvent, for example dichloromethane, at a temperature of between -60 and 20°C .

25 When R_1 is a hydrogen, the intermediate (II) and also the intermediate (II') may be prepared according to a method described in patent FR 99 11679.

30 The quinolypropylpiperidine derivative of general formula (II) for which R_1 is a fluorine atom may be prepared by oxidation of the quinolypropylpiperidine derivative of general formula (V):

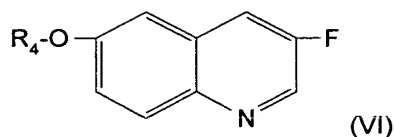


in which Rz represents an amino-protecting radical,
 optional protection of the carboxyl radical thus
 5 obtained, then, where appropriate, after protection of
 the ketone, reduction of the carboxyl radical or of the
 protected carboxyl radical to a hydroxymethyl radical
 and conversion thereof to a carboxymethyl radical as
 described above, protection of the latter and freeing
 10 of the ketone and of the amine.

The oxidation of the derivative of formula (V) is
 preferably carried out in two stages: first of all, the
 diol is obtained by oxidation of the vinyl group with
 15 potassium osmate dihydrate and 4-methylmorpholine
 N-oxide in a mixture of dichloromethane and water at a
 temperature of between 0°C and the reflux temperature
 of the solvent, preferably at 30°C, and then the diol
 is oxidized with potassium permanganate and sodium
 20 metaperiodate in a mixture of acetonitrile and water at
 a temperature of between 0°C and the reflux temperature
 of the solvent, preferably at 0°C. The protections and
 deprotections of the carboxyl, of the ketone and of the
 amine are carried out using the usual methods, where
 25 appropriate, as described above.

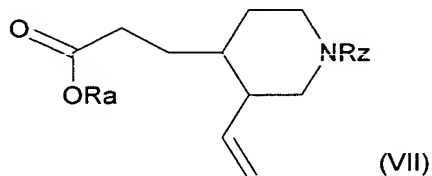
The reduction of the carboxyl or of the protected
 carboxyl and also the conversion of the hydroxymethyl
 to carboxymethyl are also carried out by the methods
 30 described above.

According to the invention, the quinolypropyl-
 piperidine derivative of general formula (V) is
 obtained by condensing the derivative which is
 35 lithiated in the 4-position of the quinoline (VI):



with a piperidine derivative of general formula (VII):

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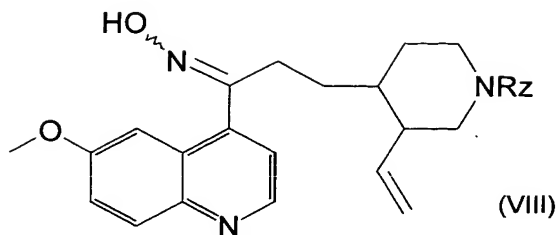


10 in which Rz is an amine-protecting group defined above and Ra is an alkyl group containing from 1 to 4 carbon atoms, preferably a methyl.

The formation of the derivative which is lithiated in the 4-position of the quinoline (VI) is carried out using a strong lithiated base such as butyllithium, 15 sec-butyllithium, or preferably lithium diisopropylamide, in a solvent such as an ether or tetrahydrofuran, at a temperature of between -78°C and -40°C. The condensation of this lithiated derivative of quinoline with the ester (VII) is carried out in the 20 same solvent, at a temperature of between -78°C and 0°C.

The quinoline derivative (VI) may be prepared according to the method described in patent application 25 WO 200240474.

The piperidine derivative of general formula (VII) may be prepared by Beckmann rearrangement of the oxime (VIII)



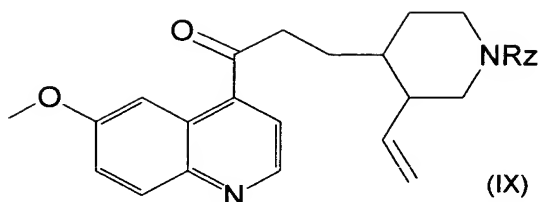
followed by cleavage of the amide thus obtained to acid,
then esterification of this acid by conventional methods
5 described in the literature.

The Beckmann rearrangement of the oxime (VIII) to amide
can be carried out according to the methods described
in the literature (M. Smith, J. March, Advanced Organic
10 Chemistry, 5th edition, p. 1415) for example by reac-
tion of a sulfonic acid chloride (such as para-toluene
sulfonyl chloride) with the oxime in a solvent such as
aqueous acetone or dichloromethane in the presence of a
base such as aqueous sodium hydroxide or potassium
15 hydroxide or an amine such as triethylamine or
diisopropylethylamine for example, at a temperature of
between 20°C and the reflux temperature of the solvent.

The cleavage of the amide, produced by the Beckmann
20 rearrangement, to acid can be carried out according to
conventional methods of the literature, such as basic
hydrolysis with sodium hydroxide or potassium
hydroxide, or else, for example, by treatment of the
amide with di-tert-butyl dicarbonate in dichloromethane
25 in the presence of triethylamine and of 4-dimethyl-
aminopyridine, followed by treatment with lithium
hydroxide monohydrate and an aqueous solution of
hydrogen peroxide using tetrahydrofuran as solvent for
example.

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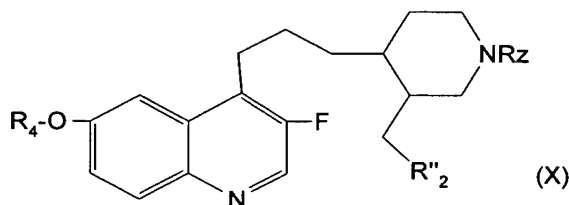
The oxime (VIII) may be obtained from the quinolyl-
propylpiperidine derivative of general formula (IX):



by reaction with hydroxylamine hydrochloride in pyridine
or else in a mixture of water and alcohol, such as
5 methanol, in the presence of a base such as sodium acetate
for example.

The quinolylpropylpiperidine derivative of general
formula (IX) may be prepared using the method described
10 in patent application FR 2354771.

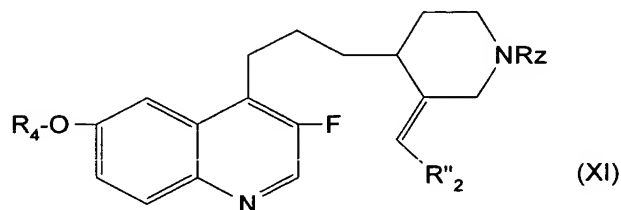
When R_1 is a fluorine and R'_2 is a carboxymethyl, the
quinolylpropylpiperidine derivative of general
formula (II') may be prepared by oxidation in basic
15 medium of the quinolylpropylpiperidine derivative of
general formula (X):



20 in which R_4 is as defined above, R_z is an amino-
protecting group, and R''_2 is the protected carboxyl
radical corresponding to R'_2 , then deprotection of the
amino. The oxidation is carried out by the action of
oxygen, preferably in an inert solvent such as dimethyl
25 sulfoxide, in the presence of tert-butanol and of a
base such as potassium or sodium tert-butoxide, at a
temperature of between 0 and 100°C. The deprotection of
the amine functional group of the piperidine is carried
out according to the conventional methods recalled
30 above.

The quinolypropylpiperidine derivative of general formula (X) may be prepared by selective hydrogenation of the quinolypropylpiperidine derivative of general formula (XI):

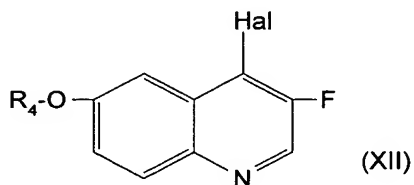
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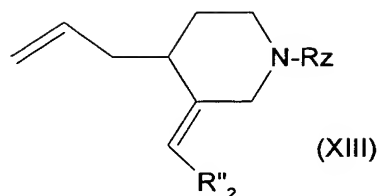
in which R_4 , R_z and R''_2 are as defined above, under a pressure of 1 to 100 bar and at a temperature of between 20 and 80°C, in a solvent such as an alcohol, ethanol for example, or an amide, dimethylformamide for example, in the presence of a catalyst, for example palladium on charcoal or palladium on barium sulfate.

The protective radical is more particularly the benzyl-oxycarbonyl radical. In this case, the hydrogenation reaction leads directly to deprotection of the amine.

The quinolypropylpiperidine derivative of general formula (XI) may be prepared by condensing a quinoline derivative of general formula (XII):



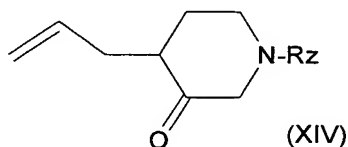
in which R_4 is as defined above and Hal represents an iodine or bromine atom, with a piperidine derivative of general formula (XIII):



in which R''_2 and Rz are as defined above.

5 The reaction is carried out by the successive action of
 an organoborane (9-borabicyclo[3.3.1]nonane for
 example) in a solvent such as an ether (tetrahydro-
 furan, dioxane for example) at a temperature of between
 -20 and 20°C, followed by the addition of the quinoline
 10 derivative of general formula (VII), by analogy with
 the methods described by Suzuki et al., Pure and Appl.
 Chem., 57, 1749 (1985). The reaction is generally
 carried out in the presence of a palladium salt
 (palladiumdiphenylphosphinoferrocene chloride for
 15 example) and of a base such as potassium phosphate, at
 a temperature of between 20°C and the reflux tempera-
 ture of the solvent.

The piperidine derivative of general formula (XIII) may
 20 be prepared by the Wittig reaction, by condensing a
 phosphorus ylide with a piperidine derivative of
 general formula (XIV):



25 in which Rz is as defined above.

The procedure is advantageously carried out using
 methyl (triphenylphosphoranylidene)acetate, in a sol-
 30 vent such as for example toluene, at a temperature of
 between 20 and 110°C.

The 3-oxopiperidine derivative of general formula (XIV) may be prepared according to or by analogy with the method described by Y. Takeuchi et al., Synthesis, 10, 1814 (1999).

5

The quinoline derivative of general formula (XII) in which R1 represents a fluorine atom may be prepared according to the method described in patent WO 200240474-A2.

10

The quinolypropylpiperidine derivative of general formula (II') for which R'₂ is a protected carboxyl radical may be prepared from the corresponding derivative for which R'₂ is a protected carboxymethyl radical, the hydroxyl in the alpha-position of the quinoline being protected, by reducing this radical to an alcohol, converting to a p-toluenesulfonyloxyethyl derivative and then converting this derivative to a vinyl derivative by an elimination reaction followed by the oxidation of the derivative obtained, and then deprotection of the alcohol functional group in the alpha-position of the quinoline and deprotection of the carboxyl radical.

25 The reduction of the protected acid to a hydroxyethyl radical is carried out according to the usual methods which do not adversely affect the rest of the molecule, in particular the reaction is carried out by action of a hydride, lithiumaluminum hydride or diisobutylaluminum hydride, for example, in a solvent such as an ether, for example tetrahydrofuran, at a temperature of between 20 and 60°C.

35 The conversion of the hydroxyethyl derivative to a para-toluenesulfonyloxyethyl derivative is carried out in particular according to the method described by L.F. Fieser and M. Fieser, Reagents for Organic Synthesis, vol. 1, 1179 (1967), using p-toluenesulfonyl chloride in the presence of a base such as a tertiary

amine, for example triethylamine, or an aromatic amine, for example pyridine, in a halogenated solvent, for example dichloromethane, or without solvent, at a temperature of between 0 and 50°C.

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The conversion of the p-toluenesulfonyloxyethyl derivative to a vinyl derivative is carried out by an elimination reaction, in particular according to the method described by A. Sharma et al., Org. Prep. 10
Proced. Int., 25(3), 330-333 (1993), in the presence of a base, for example potassium t-butoxide, in a solvent, for example dimethylsulfoxide, at a temperature of between 20 and 100°C.

15 The conversion of the vinyl derivative to a carboxyl derivative is carried out by the oxidation methods described in the literature, in particular using sodium metaperiodate in the presence of ruthenium trichloride hydrate, in a mixture of solvents such as for example 20
the water/acetonitrile mixture, at a temperature of between 20 and 60°C.

It is understood that the derivatives of general formula (I), but also the intermediates of 25
formulae (II) and (II'), (III) and (III'), (V), (VIII), (IX) and (X), and also several of the corresponding starting materials, exhibit "cis/trans" isomerism at the level of the substituents in the 3- and 4- position of piperidine. The derivatives having the "trans" 30
configuration may be obtained from the derivatives having the "cis" configuration according to or by analogy with the method described in international application WO 99/37635, or from intermediates which exist in the form of mixtures, after separation 35
according to known methods.

The quinolypropylpiperidine derivatives of general formula (I) may be purified, where appropriate by physical methods such as crystallization or

chromatography.

Moreover, it is also understood that the compounds of general formula (I) also exist in enantiomeric and diastereoisomeric forms, which forms, and also their mixtures, fall within the context of the present invention. The latter may be, where appropriate, separated in particular by chromatography on silica or by High-Performance Liquid Chromatography (HPLC). Likewise, the cis and trans derivatives may be separated by chromatography on silica or by High-Performance Liquid Chromatography (HPLC).

The quinolypropylpiperidine derivatives of general formula (I) may be converted to addition salts with acids, by known methods. It is understood that these salts also fall within the scope of the present invention.

As examples of addition salts with pharmaceutically acceptable acids, there may be mentioned the salts formed with inorganic acids (hydrochlorides, hydrobromides, sulfates, nitrates, phosphates) or with organic acids (succinates, fumarates, tartarates, acetates, propionates, maleates, citrates, methanesulfonates, ethanesulfonates, phenylsulfonates, p-toluenesulfonates, isethionates, naphthylsulfonates or camphorsulfonates, or with substitution derivatives of these compounds).

Some of the quinolypropylpiperidine derivatives of general formula (I) carrying a carboxyl radical may be converted to the form of metal salts or to addition salts with the nitrogen bases according to methods known per se. These salts also fall within the scope of the present invention. The salts may be obtained by the action of a metal base (for example an alkali or alkaline-earth metal), of ammonia or of an amine, on a product according to the invention, in an appropriate

solvent such as an alcohol, an ether or water, or by an exchange reaction with a salt of an organic acid. The salt formed precipitates after optional concentration of the solution, it is separated by filtration, 5 decantation or freeze-drying. As examples of pharmaceutically acceptable salts, there may be mentioned the salts with alkali metals (sodium, potassium, lithium) or with alkaline-earth metals (magnesium, calcium), the ammonium salt, the salts of 10 nitrogen bases (ethanolamine, diethanolamine, trimethylamine, triethylamine, methylamine, propylamine, diisopropylamine, N,N-dimethylethanolamine, benzylamine, dicyclohexylamine, N-benzyl- β -phenethylamine, N,N'-dibenzylethylenediamine, 15 diphenylenediamine, benzhydrylamine, quinine, choline, arginine, lysine, leucine, dibenzylamine).

The quinolylpropylpiperidine derivatives according to the invention are particularly advantageous 20 antibacterial agents.

In vitro, on gram-positive microbes, the quinolylpropylpiperidine derivatives according to the invention have proved active at concentrations of 25 between 0.03 and 4 $\mu\text{g/ml}$ on *Meticillin-resistant Staphylococcus aureus* AS5155, also at concentrations of between 0.06 and 8 $\mu\text{g/ml}$ on *Streptococcus pneumoniae* 6254-01 and at concentrations of between 0.06 and 64 $\mu\text{g/ml}$ on *Enterococcus faecium* H983401, and on gram- 30 negative microbes they have proved active at concentrations of between 0.12 and 32 $\mu\text{g/ml}$ on *Moraxella catharrhalis* IPA152; in vivo, they have proved active on experimental infections of mice with *Straphylococcus aureus* IP8203 at doses of between 12 35 and 150 mg/kg by the subcutaneous route (CD_{50}) and for some of them at doses of between 26 and 150 mg/kg by the oral route.

Finally, the products according to the invention are

particularly advantageous because of their low toxicity. None of the products exhibited toxicity at the dose of 100 mg/kg by the subcutaneous route in mice.

5 These properties make the products, and also their salts of pharmaceutically acceptable acids and bases, suitable for use as medicaments in the treatment of ailments involving sensitive microorganisms caused by
10 gram (+) bacteria, and in particular in that of staphylococcic infections, such as staphylococcal septicemias, malignant staphylococcic infections of the face or skin, pyoderma, septic or suppurant wounds, anthrax, phlegmons, erysipelas, acute primary or post-
15 influenza staphylococcic infections, bronchopneumonias or pulmonary suppurations.

These products can also be used as medicaments in the treatment of colibacillooses and related infections, in
20 infections with proteus, with klebsiella and with salmonella, and in other ailments caused by gram (-) bacteria.

A subject of the present invention is therefore also,
25 as medicaments, and in particular medicaments intended for the treatment of bacterial infections in humans or animals, the compounds of formula (I) as defined above, and also their pharmaceutically acceptable salts, and in particular the preferred compounds mentioned above.

30 The present invention also relates to the pharmaceutical compositions containing at least one quinolyl-propylpiperidine derivative according to the invention, where appropriate in the form of a salt, in the pure
35 state or in the form of a combination with one or more compatible and pharmaceutically acceptable diluents or adjuvants.

The compositions according to the invention can be used

orally, parenterally, topically, rectally or as aerosols.

As solid compositions for oral administration, use may
5 be made of tablets, pills, gelatin capsules, powders or
granules. In these compositions, the active product
according to the invention is mixed with one or more
inert diluents or adjuvants, such as sucrose, lactose
or starch. These compositions can comprise substances
10 other than diluents, for example a lubricant such as
magnesium stearate or a coating intended for controlled
release.

As liquid compositions for oral administration, use may
15 be made of pharmaceutically acceptable solutions,
suspensions, emulsions, syrups and elixirs containing
inert diluents such as water or paraffin oil. These
compositions can also comprise substances other than
diluents, for example wetting, sweetening or flavoring
20 products.

The compositions for parenteral administration can be
sterile solutions or emulsions. As a solvent or
vehicle, use may be made of water, propylene glycol, a
25 polyethylene glycol, plant oils, in particular olive
oil, and injectable organic esters, for example ethyl
oleate. These compositions can also contain adjuvants,
in particular wetting agents, isotonicity agents,
emulsifiers, dispersing agents and stabilizers.

30 The sterilization can be carried out in several ways,
for example using a bacteriological filter, by
irradiation or by heating. They can also be prepared in
the form of sterile solid compositions which can be
35 dissolved at the time of use in sterile water or any
other injectable sterile medium.

The compositions for topical administration can be, for
example, creams, ointments, lotions or aerosols.

The compositions for rectal administration are suppositories or rectal capsules, which contain, besides the active principle, excipients such as cocoa butter,
5 semi-synthetic glycerides or polyethylene glycols.

The compositions can also be aerosols. For use in the form of liquid aerosols, the compositions can be stable sterile solutions or solid compositions dissolved at
10 the time of use in apyrogenic sterile water, in serum or in any other pharmaceutically acceptable vehicle. For use in the form of dry aerosols intended to be inhaled directly, the active principle is finely divided up and combined with a water-soluble solid
15 diluent or vehicle with a particle size of 30 to 80 μm , for example dextran, mannitol or lactose.

In human therapy, the novel quinolypropylpiperidine derivatives according to the invention are particularly
20 useful in the treatment of infections of bacterial origin. The doses depend on the desired effect and the duration of treatment. The physician will determine the dosage which he or she estimates to be the most suitable as a function of the treatment, as a function
25 of age, of weight, and of the degree of the infection, and of other factors specific to the individual to be treated. Generally, the doses are between 750 mg and 3 g of active product taken in 2 or 3 doses per day orally, or between 400 mg and 1.2 g taken intravenously
30 for an adult.

The following example illustrates a composition according to the invention.

35 According to the usual technique, a liquid composition intended for parenteral use is prepared, comprising:

- (3R,4R)-4-[3-(3-fluoro-6-methoxy
quinolin-4-yl)-3-oxopropyl]-

1-[3-(2,3,5-trifluorophenylthio)
prop-2-ynyl]piperidine-

3-carboxylic acid..... 1 g

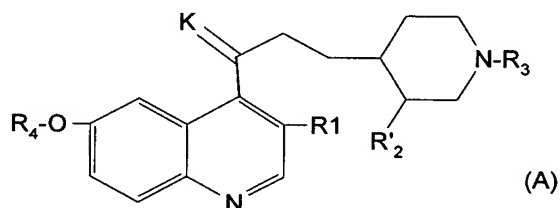
- glucose..... qs 2.5%
- 5 • sodium hydroxide..... qs pH = 4-4.5
- water for injectable preparation..... qs 20 ml

qs = in sufficient quantities up to

Finally, a subject of the invention is, as novel
industrial products, and in particular as intermediate
10 products required for the preparation of the products
of formula (I):

- the products of formula (II) as defined above,
in which R_1 is a fluorine atom and the ketone
15 is free or protected;

- the products of formula (A):

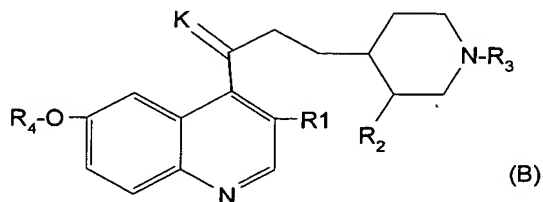


20

in which R_1 , R'_2 , R_3 and R_4 are as defined above
and K represents a ketone-protecting group;

- the products of formula (B):

25

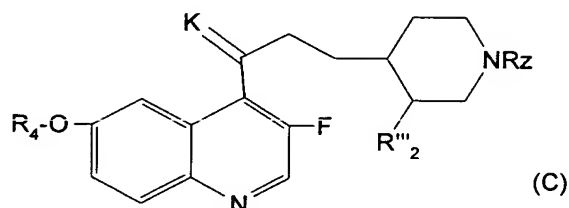


in which R_1 , R_2 , R_3 and R_4 are as defined above
and K represents a ketone-protecting group,
30 corresponding to products obtained at the end
of various treatments carried out on the

products of formula (III);

- the products of formula (V) as defined above;

5 - the products of formula (C):



10 in which R_4 , R_z and K are as defined above and R'''_2 represents a free or protected carboxyl or carboxymethyl radical or a hydroxymethyl radical, corresponding to products obtained at the end of the various treatments carried out on the products of formula (V);

15

- the products of formula (VII) as defined above;

- the products of formula (VIII) as defined above.

20 Among the products according to the invention, those which are more particularly advantageous are the quinolypropylpiperidine derivatives mentioned below, and in particular those described in the examples, in a non-limiting manner:

25

- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-(2-phenylthioethyl)piperidine-3-carboxylic acid

30 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(3-fluorophenylthio)ethyl]-piperidine-3-carboxylic acid

35 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(2,5-difluorophenylthio)ethyl]-

piperidine-3-carboxylic acid

- 5 • 3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(3,5-difluorophenylthio)ethyl]-piperidine-3-carboxylic acid
- 10 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(2,3,5-trifluorophenylthio)ethyl]-piperidine-3-carboxylic acid
- 15 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(n-propylthio)ethyl]piperidine-3-carboxylic acid
- 20 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(n-butylthio)ethyl]piperidine-3-carboxylic acid
- 25 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(cyclopropylthio)ethyl]piperidine-3-carboxylic acid
- 30 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(cyclobutylthio)ethyl]piperidine-3-carboxylic acid
- 35 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(cyclopentylthio)ethyl]piperidine-3-carboxylic acid
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(thien-2-yl)thioethyl]piperidine-3-carboxylic acid
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-

4-yl)propyl]-1-[2-(5-fluorothien-2-yl)thioethyl]-
piperidine-3-carboxylic acid

- 5 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(4-fluorothien-2-yl)thioethyl]-piperidine-3-carboxylic acid
- 10 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(3-fluorothien-2-yl)thioethyl]-piperidine-3-carboxylic acid
- 15 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(thien-3-yl)thioethyl]piperidine-3-carboxylic acid
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(1,3-thiazol-2-yl)thioethyl]-piperidine-3-carboxylic acid
- 20 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(pyridin-2-yl)thioethyl]piperidine-3-carboxylic acid
- 25 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(4-fluoropyridin-2-yl)thioethyl]-piperidine-3-carboxylic acid
- 30 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(3-fluoropyridin-2-yl)thioethyl]-piperidine-3-carboxylic acid
- 35 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(3-fluorophenyl)prop-2-ynyl]-piperidine-3-carboxylic acid
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(2,5-difluorophenyl)prop-2-ynyl]-piperidine-3-carboxylic acid

- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(3,5-difluorophenyl)prop-2-ynyl]-piperidine-3-carboxylic acid
- 5 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(2,3,5-trifluorophenyl)prop-2-ynyl]-piperidine-3-carboxylic acid
- 10 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(thien-2-yl)prop-2-ynyl]piperidine-3-carboxylic acid
- 15 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(5-fluorothien-2-yl)prop-2-ynyl]-piperidine-3-carboxylic acid
- 20 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(4-fluorothien-2-yl)prop-2-ynyl]-piperidine-3-carboxylic acid
- 25 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-(2-phenylthioethyl)-piperidine-3-carboxylic acid
- 30 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(3-fluorophenylthio)ethyl]piperidine-3-carboxylic acid
- 35 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(2,5-difluorophenylthio)ethyl]piperidine-3-carboxylic acid
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(3,5-difluorophenylthio)ethyl]piperidine-3-carboxylic acid

- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(2,3,5-trifluorophenylthio)ethyl]piperidine-3-carboxylic acid
5
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(n-propylthio)-ethyl]piperidine-3-carboxylic acid
- 10 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(n-butylthio)-ethyl]piperidine-3-carboxylic acid
- 15 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(cyclopropylthio)ethyl]piperidine-3-carboxylic acid
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(cyclobutylthio)ethyl]piperidine-3-carboxylic acid
20
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(cyclopentylthio)ethyl]piperidine-3-carboxylic acid
25
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(cyclohexylthio)-ethyl]piperidine-3-carboxylic acid
- 30 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(thien-2-yl)thioethyl]piperidine-3-carboxylic acid
- 35 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(5-fluorothien-2-yl)thioethyl]piperidine-3-carboxylic acid
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(4-fluorothien-

2-yl)thioethyl]piperidine-3-carboxylic acid

- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(3-fluorothien-2-yl)thioethyl]piperidine-3-carboxylic acid
5
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(thien-3-yl)-thioethyl]piperidine-3-carboxylic acid
10
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(1,3-thiazol-2-yl)thioethyl]piperidine-3-carboxylic acid
15
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(pyridin-2-yl)-thioethyl]piperidine-3-carboxylic acid
20
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(4-fluoropyridin-2-yl)thioethyl]piperidine-3-carboxylic acid
25
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(3-fluoropyridin-2-yl)thioethyl]piperidine-3-carboxylic acid
30
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[3-(3-fluorophenyl)-prop-2-ynyl]piperidine-3-carboxylic acid
35
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[3-(2,5-difluorophenyl)prop-2-ynyl]piperidine-3-carboxylic acid
40
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[3-(3,5-difluorophenyl)prop-2-ynyl]piperidine-3-carboxylic acid
45
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[3-(2,6-difluorophenyl)prop-2-ynyl]piperidine-3-carboxylic acid
50

6-methoxyquinolin-4-yl)propyl]-1-[3-(2,3,5-trifluoro-phenyl)prop-2-ynyl]piperidine-3-carboxylic acid

- 5 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[3-(thien-2-yl)prop-2-ynyl]piperidine-3-carboxylic acid
- 10 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[3-(5-fluorothien-2-yl)prop-2-ynyl]piperidine-3-carboxylic acid
- 15 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[3-(4-fluorothien-2-yl)prop-2-ynyl]piperidine-3-carboxylic acid
- 20 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[3-(3-fluorothien-2-yl)prop-2-ynyl]piperidine-3-carboxylic acid
- 25 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[3-(thien-3-yl)prop-2-ynyl]piperidine-3-carboxylic acid
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-(2-phenylthioethyl)piperidine-3-acetic acid
- 30 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(3-fluorophenylthio)ethyl]-piperidine-3-acetic acid
- 35 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(2,5-difluorophenylthio)ethyl]-piperidine-3-acetic acid
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(3,5-difluorophenylthio)ethyl]-piperidine-3-acetic acid

- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(2,3,5-trifluorophenylthio)ethyl]-piperidine-3-acetic acid
- 5 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(n-propylthio)ethyl]piperidine-3-acetic acid
- 10 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(n-butylthio)ethyl]piperidine-3-acetic acid
- 15 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(cyclopropylthio)ethyl]piperidine-3-acetic acid
- 20 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(cyclobutylthio)ethyl]piperidine-3-acetic acid
- 25 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(cyclohexylthio)ethyl]piperidine-3-acetic acid
- 30 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(thien-2-yl)thioethyl]piperidine-3-acetic acid
- 35 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(5-fluorothien-2-yl)thioethyl]-piperidine-3-acetic acid
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(4-fluorothien-2-yl)thioethyl]-piperidine-3-acetic acid

- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(3-fluorothien-2-yl)thioethyl]-piperidine-3-acetic acid
5
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(thien-3-yl)thioethyl]piperidine-3-acetic acid
- 10 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(1,3-thiazol-2-yl)thioethyl]-piperidine-3-acetic acid
- 15 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(pyridin-2-yl)thioethyl]piperidine-3-acetic acid
- 20 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(4-fluoropyridin-2-yl)thioethyl]-piperidine-3-acetic acid
- 25 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(3-fluoropyridin-2-yl)thioethyl]-piperidine-3-acetic acid
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(3-fluorophenyl)prop-2-ynyl]-piperidine-3-acetic acid
- 30 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(2,5-difluorophenyl)prop-2-ynyl]-piperidine-3-acetic acid
- 35 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(3,5-difluorophenyl)prop-2-ynyl]-piperidine-3-acetic acid
- (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(2,3,5-trifluorophenyl)prop-

2-ynyl]piperidine-3-acetic acid

- 5 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(thien-2-yl)prop-2-ynyl]piperidine-3-acetic acid
- 10 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(5-fluorothien-2-yl)prop-2-ynyl]piperidine-3-acetic acid
- 15 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(4-fluorothien-2-yl)prop-2-ynyl]piperidine-3-acetic acid
- 20 • (3RS,4RS) or (3SR,4RS)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(thien-3-yl)prop-2-ynyl]piperidine-3-acetic acid

Example 1

- 25 **(3R,4R)-1-(2-Cyclohexylsulfanylethyl)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]piperidine-3-carboxylic acid**

30 A solution of 0.084 g (0.163 mmol) of methyl (3R,4R)-1-(2-cyclohexylsulfanylethyl)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]piperidine-3-carboxylate in 4.5 cm³ of 5N hydrochloric acid is heated at a temperature in the region of 80°C for 5 hours. After the heating has been stopped and the mixture has returned to ambient temperature, 10 cm³ of CH₂Cl₂ and 5 cm³ of water are successively added. A 5N aqueous sodium hydroxide solution is then added, followed by a 1N solution, in order to adjust the pH of the aqueous phase to a value in the region of 8. The organic phase

is separated after settling out and the aqueous phase is then extracted with two times 15 cm³ of CH₂Cl₂. The organic phases are combined, dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) to give 0.073 g of an orange oil which is purified by flash chromatography [eluent: dichloromethane/methanol/acetonitrile (92/4/4 by volume)]. After concentrating the fractions under reduced pressure, 0.03 g of (3R,4R)-1-(2-cyclohexylsulfanylethyl)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]piperidine-3-carboxylic acid, in the form of a yellow oil, is obtained.

¹H NMR spectrum (300 MHz, (CD₃)₂SO d₆, δ in ppm): 1.25 (mt : 5H); from 1.50 to 1.98 (mt : 10H); 2.28 (mt : 1H); 2.42 (d, J = 12 Hz : 1H); from 2.50 to 2.80 (mt : 6H); 2.88 (mt : 1H); 3.06 (broad t: 1H); 3.15 (mt : 2H); 3.92 (s : 3H); 7.10 (d, J = 3 Hz : 1H); 7.50 (dd, J = 9 and 3 Hz : 1H); 8.05 (d, J = 9 Hz : 1H); 8.90 (s : 1H).

MS (EI) spectrum m/z 503 (M+H)⁺

The methyl (3R,4R)-1-(2-cyclohexylsulfanylethyl)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]piperidine-3-carboxylate may be prepared in the following way:

1.66 g of potassium carbonate, 0.665 g of potassium iodide and then a solution of 0.738 g of 2-chloroethylcyclohexyl sulfide in 10 cm³ of acetonitrile are added, at a temperature in the region of 20°C, under an argon atmosphere, to 1.5 g (4 mmol) of methyl (3R,4R)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]piperidine-3-carboxylate in solution in 20 cm³ of acetonitrile and 0.8 cm³ of dimethylformamide. After stirring for 16 hours at reflux and cooling the reaction mixture, 20 cm³ of water are added and the mixture is then concentrated to dryness under reduced

pressure (2.7 kPa). The residue is taken up with 70 cm³ of CH₂Cl₂, and washed with 2 times 35 cm³ of water then 40 cm³ of a saturated aqueous sodium chloride solution. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) to give 2.2 g of an orange oil which is purified by flash chromatography [eluent: dichloromethane/methanol/acetonitrile (98/1/1 by volume)]. After concentrating the fractions under reduced pressure, 0.67 g of an orange oil is obtained, which is purified by flash chromatography [eluent: dichloromethane/methanol/acetonitrile (98/2/2 by volume)]. After concentrating the fractions under reduced pressure, 0.495 g of methyl (3R,4R)-1-(2-cyclohexylsulfanylethyl)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]piperidine-3-carboxylate, in the form of an orange oil, is obtained.

MS (EI) spectrum m/z 516 (M+.) m/z 387 (base peak)

The methyl (3R,4R)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]piperidine-3-carboxylate may be prepared in the following way:

9 cm³ of a 4N solution of hydrochloric acid in ethyl acetate and 10 cm³ of MeOH are added, at a temperature in the region of 20°C, to 4 g (7.23 mmol) of methyl (3R,4R)-1-tert-butyloxycarbonyl-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]piperidine-3-carboxylate in solution in 20 cm³ of ethyl acetate. After stirring for 4 hours at a temperature in the region of 20°C, the reaction mixture is diluted with 25 cm³ of ethyl acetate and a 5N aqueous sodium hydroxide solution is then added in order to adjust the pH of the aqueous phase to a value of between 8 and 8.5. The organic phase is separated after settling out and the aqueous phase is then extracted with 3 times 40 cm³ of ethyl acetate. The organic phases are pooled, washed with 2 times 50 cm³ of a saturated aqueous sodium chloride

solution, dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) to give 2.33 g of methyl (3R,4R)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]-piperidine-3-carboxylate in the form of an orange oil.

MS (EI) spectrum m/z 374, (M+.)

The methyl (3R,4R)-1-*tert*-butyloxycarbonyl-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]-piperidine-3-carboxylate may be prepared in the following way:

1.58 cm³ of a thionyl chloride solution are added, at a temperature in the region of 20°C, under an argon atmosphere, to 3.33 g (7.23 mmol) of (3R,4R)-1-*tert*-butyloxycarbonyl-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]piperidine-3-carboxylic acid in solution in 150 cm³ of dichloromethane. After stirring for 1 hour at a temperature in the region of 20°C, the reaction mixture is poured over a solution of 10.55 cm³ of N,N-diisopropylethylamine in 150 cm³ of methanol. After stirring for 16 hours at a temperature in the region of 20°C, the reaction mixture is concentrated to dryness under reduced pressure (2.7 kPa). The residue is taken up with 150 cm³ of CH₂Cl₂, and washed with 3 times 50 cm³ of water and then 50 cm³ of a saturated aqueous sodium chloride solution. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) to give 4 g of methyl (3R,4R)-1-*tert*-butyloxycarbonyl-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]piperidine-3-carboxylate in the form of an orange oil.

MS (IC) spectrum m/z 475, (M+H)+

The (3R,4R)-1-*tert*-butyloxycarbonyl-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]piperidine-3-car-

boxylic acid may be prepared in the following way:

0.147 g of potassium permanganate and then a solution of 4.15 g of sodium metaperiodate in 16 cm³ of acetonitrile and 26 cm³ of water are added successively, at a temperature in the region of 0°C under an argon atmosphere, to 3.7 g (7.76 mmol) of (3R,4R)-1-*tert*-butyloxycarbonyl-3-(1RS,2-dihydroxyethyl)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxo-propyl]piperidine in solution in 200 cm³ of acetonitrile and 5 cm³ of water. After stirring for 2 hours at a temperature in the region of 0°C, 100 cm³ of a saturated aqueous sodium sulfite solution are added. After stirring for 2 hours at a temperature in the region of 20°C, the reaction medium is filtered over Celite® through a sintered glass funnel. The Celite® is rinsed with 2 times 20 cm³ of acetonitrile. The pH of the filtrate is adjusted to a value of between 4 and 5 by adding acetic acid. The filtrate is then concentrated to dryness under reduced pressure (2.7 kPa). The residue is taken up with 150 cm³ of CH₂Cl₂, and washed with 2 times 50 cm³ of water then 75 cm³ of a saturated aqueous sodium chloride solution. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) to give 3.33 g of (3R,4R)-1-*tert*-butyloxycarbonyl-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxo-propyl]piperidine-3-carboxylic acid in the form of a yellow foam.

MS (IC) spectrum m/z 461, (M+H)+

The (3R,4R)-1-*tert*-butyloxycarbonyl-3-(1RS,2-dihydroxyethyl)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxo-propyl]piperidine may be prepared in the following way:

1.3 g of 4-methylmorpholine N-oxide and then 0.0562 g of potassium osmate dihydrate are added successively, at a temperature in the region of 30°C, under an argon

atmosphere, to 2.47 g (5.02 mmol) of (3R,4R)-1-*tert*-butyloxycarbonyl-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]-3-vinylpiperidine in solution in 56.2 cm³ of dichloromethane and 1.25 cm³ of water. After stirring for 15 hours at a temperature in the region of 30°C, 100 cm³ of a saturated aqueous sodium sulfite solution are added. After stirring for 10 minutes at a temperature in the region of 20°C, the organic phase is separated after settling out and then filtered over Celite[®] through a sintered glass funnel. The Celite[®] is rinsed with 2 times 10 cm³ of dichloromethane. The pH of the filtrate is adjusted to a value in the region of 7 by adding acetic acid. The filtrate is then washed with 2 times 20 cm³ of a saturated aqueous sodium chloride solution. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) to give 3.1 g of an orange oil which is purified by flash chromatography [eluent: dichloromethane/methanol/acetonitrile (98/2/2 by volume)]. After concentrating the fractions under reduced pressure, 1.9 g of (3R,4R)-1-*tert*-butyloxycarbonyl-3-(1RS,2-dihydroxyethyl)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]-piperidine, in the form of a yellow oil, are obtained.

MS (IC) spectrum m/z 477, (M+H)+

The (3R,4R)-1-*tert*-butyloxycarbonyl-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]-3-vinylpiperidine may be prepared in the following way:

15.9 cm³ of a solution of 1.6M *n*-butyl lithium (nBuLi)/hexane are added, at a temperature in the region of -78°C, under an argon atmosphere, to 3.57 cm³ (25.4 mmol) of diisopropylamine in solution in 20 cm³ of tetrahydrofuran. After returning to a temperature in the region of 0°C for a period of 10 minutes, the reaction medium is again cooled to a temperature in the region of -78°C. A solution of 2.97 g (16.8 mmol) of

3-fluoro-6-methoxyquinoline in 40 cm³ of tetrahydrofuran is then added under an argon atmosphere. After stirring for 4 hours at a temperature in the region of -78°C and then returning to a temperature in the region of -40°C, a solution of 6 g (17.6 mmol) of (3R,4R)-1-tert-butyloxycarbonyl-4-(2-methoxycarbonylethyl)-3-vinylpiperidine in 40 cm³ of tetrahydrofuran is added under an argon atmosphere. After stirring for 10 minutes at a temperature in the region of -40°C and then returning in 10 minutes to a temperature in the region of -10°C, 30 cm³ of a saturated aqueous solution with ammonium chloride, 30 cm³ of ethyl acetate and 30 cm³ of water are successively added. The organic phase is separated after settling out, washed successively with 2 times 40 cm³ of water and 40 cm³ of a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) to give 8 g of an orange oil which is purified by flash chromatography (eluent: dichloromethane/methanol/acetonitrile (100/0/0 then 99/0.5/0.5 by volume)]. After concentrating the fractions under reduced pressure, 2.47 g of (3R,4R)-1-tert-butyloxycarbonyl-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-oxopropyl]-3-vinylpiperidine, in the form of a yellow oil, are obtained.

MS (IC) spectrum m/z 443, (M+H)+

The (3R,4R)-1-tert-butyloxycarbonyl-4-(2-methoxycarbonylethyl)-3-vinyl-piperidine may be prepared in the following way:

50 cm³ of a solution of 2M trimethylsilyldiazomethane/hexane are added, at a temperature in the region of 15°C, under an argon atmosphere, to 5 g (17.64 mmol) of (3R,4R)-1-tert-butyloxycarbonyl-4-(2-carboxyethyl)-3-vinylpiperidine in solution in 50 cm³ of methanol. After stirring for 3 hours at a temperature in the

region of 22°C, the reaction medium is concentrated to dryness under reduced pressure (2.7 kPa) to give 5.3 g of (3R,4R)-1-*tert*-butyloxycarbonyl-4-(2-methoxycarbonylethyl)-3-vinylpiperidine in the form of an orange oil.

MS (EI) spectrum m/z 297 (M^{+}) m/z 57 (base peak)

The (3R,4R)-1-*tert*-butyloxycarbonyl-4-(2-carboxyethyl)-3-vinylpiperidine may be prepared in the following way:

2.26 cm³ of an aqueous solution of hydrogen peroxide at 9.8 mol/l and 0.310 g of lithium hydroxide monohydrate are added successively, at a temperature in the region of 20°C, under an argon atmosphere, to 2 g (3.7 mmol) of (3R,4R)-1-*tert*-butyloxycarbonyl-4-{3-[*tert*-butyloxycarbonyl-(6-methoxyquinolin-4-yl)amino]-3-oxopropyl}-3-vinylpiperidine in solution in 56 cm³ of tetrahydrofuran and 18 cm³ of water. After stirring for 16 hours, 50 cm³ of a saturated aqueous sodium sulfite solution are added and the tetrahydrofuran is then evaporated off under reduced pressure (2.7 kPa). The aqueous phase is filtered and the residue is washed with 3 times 30 cm³ of water. The filtrates are pooled, acidified to a pH in the region of 3.5 by adding acetic acid and then extracted with 3 times 40 cm³ of dichloromethane. The organic phases are pooled, dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) to give 0.9 g of (3R,4R)-1-*tert*-butyloxycarbonyl-4-(2-carboxyethyl)-3-vinylpiperidine in the form of a colorless oil.

MS (IC) spectrum m/z 284, ($M+H$)⁺ m/z 301, ($M+NH_4$)⁺

The (3R,4R)-1-*tert*-butyloxycarbonyl-4-{3-[*tert*-butyloxycarbonyl-(6-methoxyquinolin-4-yl)amino]-3-oxopropyl}-3-vinylpiperidine may be prepared in the following way:

1.85 cm³ of triethylamine, 11.5 g of di-*tert*-butyl dicarbonate and 1.61 g of 4-(dimethylamino)pyridine are added successively, at a temperature in the region of 20°C, under an argon atmosphere, to 5.8 g (13.21 mmol) of (3R,4R)-1-*tert*-butyloxycarbonyl-4-[3-(6-methoxyquinolin-4-ylamino)-3-oxopropyl]-3-vinylpiperidine in solution in 150 cm³ of dichloromethane. After stirring for 16 hours, the reaction medium is washed successively with 2 times 200 cm³ of water then 2 times 200 cm³ of a saturated aqueous ammonium chloride solution. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) to give 8.2 g of (3R,4R)-1-*tert*-butyloxycarbonyl-4-{3-[*tert*-butyloxycarbonyl-(6-methoxyquinolin-4-yl)amino]-3-oxopropyl}-3-vinylpiperidine in the form of an orange oil.

MS (IC) spectrum m/z 540, (M+H)+

The (3R,4R)-1-*tert*-butyloxycarbonyl-4-[3-(6-methoxyquinolin-4-ylamino)-3-oxopropyl]-3-vinylpiperidine may be prepared in the following way:

1.73 g of *p*-toluenesulfonyl chloride and then a solution of 0.322 g of potassium hydroxide in 4.5 cm³ of water are added successively, at a temperature in the region of 20°C, under an argon atmosphere, to 2.5 g (5.69 mmol) of (3R,4R)-1-*tert*-butyloxycarbonyl-4-[3-[(*E,Z*)-hydroxyimino]-3-(6-methoxyquinolin-4-yl)-propyl]-3-vinylpiperidine in solution in 12.75 cm³ of acetone. After stirring for 30 minutes at reflux, the reaction medium is concentrated to dryness under reduced pressure (2.7 kPa). The residue is taken up with 100 cm³ of CH₂Cl₂ and then washed with 3 times 50 cm³ of water. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) to give 3.2 g of an orange solid which is purified by flash

chromatography [eluent: dichloromethane/methanol/acetonitrile (96/2/2 by volume)]. After concentrating the fractions under reduced pressure, 1 g of (3R,4R)-1-*tert*-butyloxycarbonyl-4-[3-(6-methoxyquinolin-4-yl-amino)-3-oxopropyl]-3-vinylpiperidine, in the form of a beige solid, is obtained.

MS (IC) spectrum m/z 440, (M+H)+

10 The (3R,4R)-1-*tert*-butyloxycarbonyl-4-[3-[(E,Z)-hydroxyimino]-3-(6-methoxyquinolin-4-yl)propyl]-3-vinylpiperidine may be prepared in the following way:

1.2 g of hydroxylamine hydrochloride and then 2.35 g of sodium acetate trihydrate are added successively, at a temperature in the region of 20°C, to 6.4 g (13.85 mmol) of (3R,4R)-1-*tert*-butyloxycarbonyl-4-[3-(6-methoxyquinolin-4-yl)-3-oxopropyl]-3-vinylpiperidine in solution in 5 cm³ of methanol and 75 cm³ of water. After stirring for 72 hours, the reaction medium is extracted with 100 cm³ then 2 times 50 cm³ of dichloromethane. The organic phases are pooled, washed with 100 cm³ of water, dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) to give 5.9 g of (3R,4R)-1-*tert*-butyloxycarbonyl-4-[3-[(E,Z)-hydroxyimino]-3-(6-methoxyquinolin-4-yl)propyl]-3-vinylpiperidine, in the form of an orange solid.

30 MS (IC) spectrum m/z 440, (M+H)+

The (3R,4R)-1-*tert*-butyloxycarbonyl-4-[3-(6-methoxyquinolin-4-yl)-3-oxopropyl]-3-vinylpiperidine may be prepared in the following way:

35

4.28 cm³ of triethylamine and then a solution of 3.43 g of di-*tert*-butyl dicarbonate in 50 cm³ of dichloromethane are added successively, at a temperature in the region of 20°C, under an argon atmosphere, to 5 g

(13.85 mmol) of (3R,4R)-4-[3-(6-methoxyquinolin-4-yl)-3-oxopropyl]-3-vinylpiperidine in solution in 100 cm³ of dichloromethane. After stirring for 16 hours, the reaction medium is washed with 3 times 150 cm³ of water. The organic phase is dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) to give 6.4 g of (3R,4R)-1-*tert*-butyloxycarbonyl-4-[3-(6-methoxyquinolin-4-yl)-3-oxopropyl]-3-vinylpiperidine in the form of an orange oil.

MS (IC) spectrum m/z 425, (M+H)+

The (3R,4R)-4-[3-(6-methoxyquinolin-4-yl)-3-oxopropyl]-3-vinylpiperidine may be prepared using the method described in patent application FR 2354771.

Example 2

(3R,4R)-4-[3-Oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)-propyl]-1-[2-(2,5-difluorophenylsulfanyl)ethyl]piperidine-3-carboxylic acid

A mixture of 0.1 g of methyl (3R,4R)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(2,5-difluorophenylsulfanyl)ethyl]piperidine-3-carboxylate in 2 cm³ of 5N hydrochloric acid is brought to a temperature in the region of 80°C with stirring and under an inert atmosphere for 5 hours. After cooling to around 20°C, the reaction medium is neutralized with 1.8 cm³ of 5N sodium hydroxide until a pH of 6 is obtained, and is then extracted with 20 cm³ of dichloromethane. The organic phase is dried over magnesium sulfate, filtered, and then evaporated to dryness under reduced pressure (2 kPa) at a temperature in the region of 30°C. The residue obtained is purified by chromatography on a column of silica gel (particle size 70-200 µm; diameter 2 cm), eluting with a mixture of dichloromethane-methanol-aqueous ammonia (28%)

(40/5/0.5 by volume) and collecting fractions of 10 cm³. The fractions containing the expected product are pooled and then evaporated according to the conditions described above. 0.072 g of (3R,4R)-
5 4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(2,5-difluorophenylsulfanyl)ethyl]piperidine-3-carboxylic acid, in the form of a beige-colored solid, is obtained.

10 ¹H NMR spectrum (300 MHz, (CD₃)₂SO d₆, δ in ppm): from 1.55 to 1.90 (mt : 5H); 2.29 (mt : 1H); 2.44 (broad d, J = 12 Hz : 1H); 2.61 (mt : 1H); 2.68 (t, J = 7 Hz : 2H); 2.79 (mt : 1H); 2.97 (mt : 1H); 3.12 (mt : 2H); 3.20 (broad t, J = 6 Hz : 2H); 3.91 (s : 3H); from 7.00
15 to 7.15 (mt : 1H); 7.09 (d, J = 3 Hz : 1H); from 7.20 to 7.40 (mt : 2H); 7.47 (dd, J = 9 and 3 Hz : 1H); 8.05 (d, J = 9 Hz : 1H); 8.89 (d, J = 0.5 Hz : 1H); from 12.80 to 13.20 (broad unresolved peak : 1H).

20 Methyl (3R,4R)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(2,5-difluorophenylsulfanyl)ethyl]-piperidine-3-carboxylate

A mixture of 0.57 g of methyl (3R,4R)-4-[3-oxo-
25 3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]piperidine-3-carboxylate obtained as described in example 1, 0.462 g of 2-(2-bromoethylsulfanyl)-1,4-difluorobenzene, 0.253 g of potassium iodide and 1.05 g of potassium carbonate in 25 cm³ of acetonitrile is heated
30 with stirring and under an inert atmosphere for 20 hours at a temperature in the region of 75°C. After cooling to a temperature in the region of 20°C, the reaction medium is filtered and the insoluble material is washed with 2 times 10 cm³ of acetonitrile. The
35 filtrate is evaporated under reduced pressure (2 kPa) at a temperature in the region of 40°C. The evaporation residue is taken up with 50 cm³ of distilled water and 100 cm³ of ethyl acetate. The organic phase is washed with 3 times 30 cm³ of distilled water and 2 times

50 cm³ of a saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated according to the conditions mentioned above. The oil obtained is purified by chromatography on a column of silica gel (particle size 70-200 µm; diameter 2.5 cm), eluting with a mixture of dichloromethane-methanol (9/10 by volume) and collecting fractions of 10 cm³. The fractions containing the expected product are pooled and then evaporated under reduced pressure (2 kPa) at a temperature in the region of 40°C. 0.4 g of methyl (3R,4R)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)-propyl]-1-[2-(2,5-difluorophenylsulfanyl)ethyl]-piperidine-3-carboxylate, in the form of an orange-colored viscous oil, is obtained.

¹H NMR spectrum (300 MHz, (CD₃)₂SO d₆, δ in ppm): 1.56 (mt : 1H); from 1.65 to 2.00 (mt : 4H); 2.24 (mt : 1H); 2.40 (broad d, J = 12 Hz : 1H); from 2.50 to 2.70 (mt : 3H); 2.72 (mt : 1H); 2.85 (mt : 1H); 3.04 (mt : 2H); 3.12 (t, J = 7 Hz : 2H); 3.57 (s : 3H); 3.90 (s : 3H); from 7.00 to 7.10 (mt : 1H); 7.09 (d, J = 3 Hz : 1H); from 7.20 to 7.35 (mt : 2H); 7.48 (dd, J = 9 and 3 Hz : 1H); 8.05 (d, J = 9 Hz : 1H); 8.89 (s : 1H).

Example 3

(3RS,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)-propyl]-1-[2-(2,5-difluorophenylsulfanyl)ethyl]piperidine-3-acetic acid

A mixture of 0.3 g of methyl (3RS,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(2,5-difluorophenylsulfanyl)ethyl]piperidine-3-acetate in 1.34 cm³ of a 1N aqueous sodium hydroxide solution and 5 cm³ of dioxane is brought to a temperature in the region of 60°C with stirring and under an inert atmosphere for 1 hour. After cooling to around 20°C, the reaction medium is evaporated to dryness under reduced pressure (2 kPa) at a temperature in the region

of 50°C. The evaporation residue obtained is taken up with 20 cm³ of water and 20 cm³ of diethyl ether, and the aqueous phase is separated after settling out and neutralized with 1.3 cm³ of 1N aqueous hydrochloric acid solution and is then extracted with 70 cm³ of ethyl acetate. The organic phase is dried over magnesium sulfate, filtered, and then evaporated according to the same conditions above. 0.23 g of (3RS,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)-propyl]-1-[2-(2,5-difluorophenylsulfanyl)ethyl]-piperidine-3-acetic acid, in the form of a beige-colored solid, is obtained.

¹H NMR spectrum (300 MHz, (CD₃)₂SO d₆, δ in ppm): 1.32 (very broad t, J = 13.5 Hz : 1H); 1.49 (broad d : J = 13.5 Hz : 1H); from 1.50 to 1.75 (mt : 3H); from 1.90 to 2.20 (mt : 3H); 2.20 (d mt, J = 16.5 Hz : 1H); 2.47 (dd, J = 16.5 and 9 Hz : 1H); from 2.50 to 2.70 (mt : 2H); 2.78 (mt : 2H); 3.06 (t, J = 7.5 Hz : 2H); 3.12 (t, J = 7 Hz : 2H); 3.90 (s : 3H); from 7.00 to 7.15 (mt : 1H); 7.10 (d, J = 3 Hz : 1H); from 7.20 to 7.35 (mt : 2H); 7.47 (dd, J = 9 and 3 Hz : 1H); 8.04 (d, J = 9 Hz : 1H); 8.88 (s : 1H).

Methyl (3RS,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(2,5-difluorophenylsulfanyl)ethyl]-piperidine-3-acetate

1.88 cm³ of dimethyl sulfoxide in 6 cm³ of dichloromethane are poured, over 10 minutes, over a solution of 1.32 cm³ of oxalyl dichloride in 30 cm³ of dichloromethane cooled to -70°C, with stirring and under an inert atmosphere. After 10 minutes, a solution of 1.7 g of methyl (3RS,4RS)-4-[3-(R,S)-hydroxy-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(2,5-difluorophenylsulfanyl)ethyl]piperidine-3-acetate in 15 cm³ of dichloromethane is poured in 10 minutes. After 15 minutes, 8.4 cm³ of triethylamine in 10 cm³ of dichloromethane are added dropwise over 15 minutes and

the reaction medium is stirred for 45 minutes in the region of -70°C and then for 20 hours in the region of 20°C . 50 cm^3 of distilled water are poured over the reaction mass, and the organic phase is separated after settling out, and washed with 50 cm^3 of a saturated aqueous sodium hydrogen carbonate solution, with 2 times 30 cm^3 of distilled water and with 30 cm^3 of saturated aqueous sodium chloride solution. The organic extract is dried over magnesium sulfate, filtered, and evaporated under reduced pressure (2 kPa) at a temperature in the region of 40°C . The residue obtained is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (particle size 40-60 μm ; diameter 3 cm), eluting with a mixture of cyclohexane-ethyl acetate (60/40 by volume) and collecting fractions of 10 cm^3 . The fractions containing the expected product are pooled and then evaporated according to the conditions described above. 1.37 g of methyl (3RS,4RS)-4-[3-oxo-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(2,5-difluorophenyl-sulfanyl)ethyl]piperidine-3-acetate are obtained.

Infrared spectrum: (CCl_4) 2930; 1737; 1701; 1621; 1506; 1484; 1468; 1232; 1189; 1166; 1028; 905 and 834 cm^{-1}

Methyl (3RS,4RS)-4-[3-(R,S)hydroxy-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(2,5-difluoro-phenyl-sulfanyl)ethyl]piperidine-3-acetate

A mixture of 6.5 g of methyl (3RS,4RS)-4-[3-(R,S)-hydroxy-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-piperidine-3-acetate dihydrochloride, 3.9 g of 2-(2-bromoethylsulfanyl)-1,4-difluorobenzene dissolved in 10 cm^3 of dimethylformamide, 2.32 g of potassium iodide, 5.8 g of potassium carbonate and 3.93 cm^3 of triethylamine in 200 cm^3 of acetonitrile is heated with stirring and under an inert atmosphere for 22 hours at a temperature in the region of 70°C . After cooling to a temperature in the region of 20°C , the reaction medium

is filtered and the insoluble material is washed with 2 times 30 cm³ of acetonitrile. The filtrate is evaporated under reduced pressure (2 kPa) at a temperature in the region of 40°C. The evaporation residue is taken up with 100 cm³ of distilled water and 150 cm³ of ethyl acetate. The organic phase is washed with 3 times 100 cm³ of distilled water and 2 times 100 cm³ of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, and evaporated according to the conditions described above. The oil obtained is purified by chromatography under an argon pressure of 50 kPa, on a column of silica gel (particle size 40-60 µm; diameter 4 cm), eluting with a mixture of cyclohexane-ethyl acetate (50/50 by volume) and collecting fractions of 60 cm³. The fractions containing the expected product are pooled and then evaporated under reduced pressure (2 kPa) at a temperature in the region of 40°C. 1.7 g of methyl (3RS,4RS)-4-[3-(R,S)-hydroxy-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-[2-(2,5-difluorophenylsulfanyl)ethyl]piperidine-3-acetate, in the form of an orange-colored viscous oil, are obtained.

¹H NMR spectrum (300 MHz, (CD₃)₂SO d₆, δ in ppm). A mixture of two diastereoisomers in 50/50 proportions is observed: from 0.90 to 2.60 (mt : 14H); from 2.60 to 2.80 (mt : 2H); 3.08 (broad t, J = 7 Hz : 2H); 3.47 and 3.55 (2 s : 3H in all); 3.89 (s : 3H); 5.33 (very broad t, J = 7 Hz : 1H); 5.83 (broad s : 1H); 7.05 (mt : 1H) ; from 7.15 to 7.35 (mt : 2H); 7.38 (d mt, J = 9 Hz : 1H) ; from 7.90 to 8.00 (mt : 2H) ; 8.68 (broad s : 1H).

Methyl (3RS,4RS) and (3SR,4RS)-4-[3-(R,S)-hydroxy-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]piperidine-3-acetate dihydrochloride

A solution of 940 mg of (3RS, 4RS) and (3SR, 4RS)-4-[3-(R,S)-hydroxy-3-(3-fluoro-6-methoxyquinolin-4-

yl)propyl]-1-(*tert*-butyloxycarbonyl)piperidine-3-acetic acid in 20 cm³ of methanol is cooled to a temperature in the region of -25°C, with stirring and under an inert atmosphere. 0.43 cm³ of thionyl chloride is added to this solution over 5 minutes. The mixture is brought back to a temperature in the region of 20°C, while the stirring is continued for a further 1 hour 30 minutes. The reaction mixture is concentrated under reduced pressure (5 kPa) at a temperature in the region of 40°C and 30 cm³ of methanol are then added. This series of operations is repeated 3 times. 920 mg of methyl (3RS,4RS) and (3SR,4RS)-4-[3-(R,S)-hydroxy-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]piperidine-3-acetate dihydrochloride, in the form of a yellow foam, are obtained.

Infrared spectrum (KBr): 3249; 1949; 2503; 2020; 1731; 1622; 1604; 1555; 1497; 1457; 1420; 1308; 1242; 1200; 1175; 1080; 1014; 872; 832 and 795 cm⁻¹

(3RS, 4RS) and (3SR,4RS)-4-[3-(R,S)-hydroxy-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-(*tert*-butyloxycarbonyl)piperidine-3-acetic acid

A solution of 1.16 g of methyl (3RS,4RS) and (3SR,4RS)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-propyl]-1-(*tert*-butyloxycarbonyl)piperidine-3-acetate, 100 cm³ of anhydrous dimethylsulfoxide and 25 cm³ of anhydrous *tert*-butanol is stirred under an inert atmosphere free of water at 20°C. This colorless solution is purged with pure oxygen until saturation of the reaction mixture is obtained. A solution containing 685 mg of potassium *tert*-butoxide in 8 cm³ of anhydrous *tert*-butanol is then added. Oxygen is again introduced by sparging for a further 3 hours 30 minutes with vigorous stirring. The yellow solution obtained is purged with nitrogen and then cooled to 0°C. 0.5 cm³ of pure acetic acid in 20 cm³ of water and then 200 cm³ of ether are subsequently added. The organic phase is separated

after settling out, washed with 7 times 20 cm³ of water and with 3 times 20 cm³ of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated under reduced pressure
5 (5 kPa) at a temperature in the region of 40°C. A gum is obtained which is taken up in 20 cm³ of ether. The mixture is again concentrated under the same conditions as above. 945 mg of (3RS,4RS) and (3SR,4RS)-4-[3-(R,S)-hydroxy-3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-1-
10 (tert-butyloxycarbonyl)piperidine-3-acetic acid, in the form of a white foam, are obtained.

Infrared spectrum (KBr): 2973; 2932; 2864; 1693; 1668; 1623; 1510; 1468; 1429; 1366; 1232; 1166; 1030 and
15 831 cm⁻¹

Infrared spectrum (CH₂Cl₂): 3600; 2982; 2939; 2867; 1710; 1682; 1623; 1509; 1468; 1429; 1367; 1231; 1162; 1030; 909; 896 and 834 cm⁻¹

20 Methyl (3RS, 4RS) and (3SR, 4RS)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-propyl]-1-(tert-butyloxy-carbonyl)piperidine-3-acetate

25 A solution of 1.85 g of methyl (3RS,4RS) and (3SR,4RS)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]-piperidine-3-acetate, 0.7 cm³ of triethylamine and 40 cm³ of dichloromethane is cooled to a temperature in the region of 0°C, with stirring and under an argon
30 atmosphere. A solution of 1.16 g of di-tert-butyl dicarbonate dissolved in 40 cm³ of dichloromethane is added to this colorless solution over 20 minutes. The mixture is returned to a temperature in the region of 20°C, while the stirring is continued for a further
35 10 hours. 200 cm³ of water are then added to the reaction mixture. The organic phase is separated after settling out, washed with 100 cm³ of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and then concentrated under reduced

pressure (5 kPa) at a temperature in the region of 40°C. An oil is obtained which is purified by chromatography, under a nitrogen pressure of 50 kPa, on a column of silica gel (particle size 20-45 μ ; diameter 2 cm; height 20 cm), eluting with a mixture of cyclohexane-ethyl acetate (70/30 by volume) and collecting fractions of 40 cm³. Fractions 8 to 12 are pooled, and then concentrated as above. 2.16 g of methyl (3RS,4RS) and (3SR,4RS)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)-3-propyl]-1-(*tert*-butoxycarbonyl)-piperidine-3-acetate, in the form of a colorless oil, are obtained.

Infrared spectrum (CCl₄) 3006; 1740; 1695; 1622; 1507; 1468; 1428; 1366; 1231; 1166; 1034; 909 and 832 cm⁻¹

Methyl (3RS,4RS) and (3SR,4RS)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]piperidine-3-acetate

2.65 g of methyl (4RS)-1-benzyloxycarbonyl-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]piperidine-3-ylideneacetate, the *Z* isomer, 45 cm³ of absolute ethanol and 265 mg of palladium on charcoal at 10% are introduced into an autoclave. The reaction mixture is stirred under 5 bar of hydrogen at 22°C for 24 hours, and then filtered over supercel and rinsed with 5 times 20 cm³ of absolute ethanol. The pooled filtrates are concentrated under reduced pressure (5 kPa) at a temperature in the region of 40°C. 1.85 g of methyl (3RS,4RS) and (3SR,4RS)-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]piperidine-3-acetate, in the form of a colorless oil, are obtained.

¹H NMR spectrum (300 MHz, (CD₃)₂SO d₆, δ in ppm).
from 1.10 to 1.80 (mt : 7H); from 1.90 to 2.30 (mt : 2H); from 2.35 to 2.60 (mt : 3H); from 2.65 to 2.95 (mt : 2H); 3.06 (mt : 2H); 3.55 and 3.56 (2s : 3H in all); 3.95 and 3.96 (2s : 3H in all); from 7.30 to 7.45 (mt : 2H); 7.96 (d, *J* = 9 Hz : 1H); 8.70 (broad s :

1H).

Methyl (4RS)-1-benzyloxycarbonyl-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]piperidine-3-ylidene
5 acetate, Z isomer.

A solution of 5.8 g of methyl (4RS)-4-allyl-1-benzyloxycarbonylpiperidin-3-ylidene acetate (Z isomer) in 15 cm³ of tetrahydrofuran is added
10 slowly, at a temperature in the region of 0°C, with stirring and under an inert atmosphere, to 45 cm³ of a 0.5 M solution of 9-borabicyclo[3,3,1]nonane in tetrahydrofuran. The mixture is then brought back to a temperature in the region of 20°C, while the stirring
15 is continued for a further 4 hours. 5.5 g of 4-iodo-3-fluoro-6-methoxyquinoline in solution in 100 cm³ of tetrahydrofuran are added, followed by 11.2 g of tripotassium phosphate, and, finally, 386 mg of palladiumdiphenylphosphinoferrocene chloride. The
20 reaction mixture is heated for 2 hours at reflux and then stirred for 48 hours at ambient temperature. The suspension obtained is filtered. The filtrate is concentrated and then taken up in 200 cm³ of ethyl acetate. The solution obtained is washed with 2 times
25 200 cm³ of water then with 2 times 200 cm³ of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and then concentrated under reduced pressure (5 kPa) at a temperature in the region of 40°C. 15 g of an oil are obtained, which is
30 purified by chromatography, under a nitrogen pressure of 50 kPa, on a column of silica gel (particle size 20-45 µ; diameter 6 cm; height 38 cm), eluting with a mixture of cyclohexane-ethyl acetate (85/15 by volume, forming a gradient up to 70/30 by volume) and
35 collecting fractions of 200 cm³. Fractions 31 to 34 are pooled and then concentrated. 4.7 g of methyl (4RS)-1-benzyloxycarbonyl-4-[3-(3-fluoro-6-methoxyquinolin-4-yl)propyl]piperidine-3-ylidene acetate (Z isomer), in the form of a colorless oil, are obtained.

Infrared spectrum (CCl₄): 3091; 3068; 3034; 1705; 1655; 1622; 1507; 1468; 1434; 1361; 1263; 1231; 1207; 1173; 1141; 1034; 909; 832 and 696 cm⁻¹

5

Methyl (4RS)-4-allyl-1-benzyloxycarbonylpiperidin-3-ylidene acetate, Z isomer.

10 A solution containing 16.3 g of (4RS)-4-allyl-1-benzyl-oxycarbonylpiperidin-3-one in 200 cm³ of toluene is stirred at reflux with methyl (triphenylphosphoranylidene) acetate, under an inert atmosphere, for 16 hours. After cooling to approximately 20°C, the reaction mixture is
15 concentrated under reduced pressure (5 kPa) at a temperature in the region of 40°C, and the residue obtained, solubilized in 50 cm³ of dichloromethane under hot conditions, is purified by chromatography, under a nitrogen pressure of 50 kPa, on a column of
20 silica gel (particle size 20-45 μ; diameter 10 cm; height 45 cm), eluting with a mixture of cyclohexane-ethyl acetate (80/20 by volume) and collecting fractions of 250 cm³. Fractions 13 to 15 are pooled and then concentrated as above. 5.8 g of methyl (4RS)-
25 4-allyl-1-benzyloxycarbonylpiperidin-3-ylidene acetate (Z isomer), in the form of a colorless oil, are obtained.

30 Infrared spectrum (CCl₄): 3068; 3034; 2949; 2853; 1722; 1705; 1655; 1643; 1434; 1260; 1200; 1174; 1144; 993; 918 and 696 cm⁻¹

The (4RS)-4-allyl-1-benzyloxycarbonylpiperidin-3-one may be prepared according to Y.Takeuchi et al.,
35 described in Synthesis 1999, 10, 1814.

Example 4

(3R,4R)-4-[3-Oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-

[2-(2-thienylsulfanyl)ethyl]piperidine-3-carboxylic acid

A mixture of 0.43 g of methyl (3R,4R)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(2-thienylsulfanyl)-ethyl]piperidine-3-carboxylate in 5 cm³ of 5N hydrochloric acid is brought to a temperature in the region of 80°C with stirring and under an inert atmosphere for 5 hours. After cooling to around 20°C, the reaction medium is neutralized with 4.7 cm³ of 5N sodium hydroxide until a pH of 6 is obtained, and is then extracted with 30 cm³ of dichloromethane. The organic phase is dried over magnesium sulfate, filtered, and then evaporated to dryness under reduced pressure (2 kPa) at a temperature in the region of 30°C. The residue obtained is purified by chromatography on a column of silica gel (particle size 70-200 µm; diameter 2 cm), eluting with a mixture of chloroform-methanol-aqueous ammonia (28%) (12/3/0.5 by volume) and collecting fractions of 10 cm³. The fractions containing the expected product are pooled and then evaporated according to the conditions described above. 0.4 g of (3R,4R)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(2-thienylsulfanyl)ethyl]piperidine-3-carboxylic acid, in the form of a yellow-colored oil, is obtained.

¹H NMR spectrum (300 MHz, (CD₃)₂SO d₆, δ in ppm): from 1.55 to 1.85 (mt : 5H); 2.35 (mt : 1H); from 2.40 to 2.50 (mt : 1H); from 2.60 to 2.75 (mt : 3H); 2.84 (mt : 1H); from 2.90 to 3.10 (mt : 3H); 3.19 (mt : 2H); 3.89 (s : 3H); 7.06 (dd, J = 6 and 3.5 Hz : 1H); 7.22 (broad d, J = 3.5 Hz : 1H); 7.48 (dd, J = 9 and 3 Hz : 1H); 7.62 (dd, J = 6 and 1 Hz : 1H); 7.73 (d, J = 3 Hz : 1H); 7.91 (d, J = 5 Hz : 1H); 8.02 (d, J = 9 Hz : 1H); 8.88 (d, J = 5 Hz : 1H).

35

Methyl (3R,4R)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(2-thienylsulfanyl)ethyl]piperidine-3-carboxylate

A mixture of 0.95 g of methyl (3R,4R)-4-[3-oxo-3-(6-

methoxyquinolin-4-yl)propyl]piperidine-3-carboxylate, 0.72 g of 2-(2-bromoethylsulfanyl)-2-thiophene, 0.44 g of potassium iodide and 1.9 g of potassium carbonate in 40 cm³ of acetonitrile is heated with stirring and
5 under an inert atmosphere for 17 hours at a temperature in the region of 70°C. After cooling to a temperature in the region of 20°C, the reaction medium is filtered and the insoluble material is washed with 2 times 15 cm³ of acetonitrile. The filtrate is evaporated
10 under reduced pressure (2 kPa) at a temperature in the region of 40°C. The evaporation residue is taken up with 50 cm³ of distilled water and 100 cm³ of ethyl acetate. The organic phase is washed with 3 times 30 cm³ of distilled water and 2 times 50 cm³ of a
15 saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated according to the conditions described above. The oil obtained is purified by chromatography on a column of silica gel (particle size 70-200 µm; diameter 2.5 cm), eluting
20 with a mixture of ethyl acetate-petroleum ether (80/20 by volume) and collecting fractions of 10 cm³. The fractions containing the expected product are pooled and then evaporated under reduced pressure (2 kPa) at a temperature in the region of 40°C. 0.43 g of methyl
25 (3R,4R)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[2-(2-thienylsulfanyl)ethyl]piperidine-3-carboxylate, in the form of a brown-colored viscous oil, is obtained.

30 ¹H NMR spectrum (300 MHz, (CD₃)₂SO d₆, δ in ppm): 1.56 (mt : 1H); from 1.60 to 1.95 (mt : 4H); 2.21 (mt : 1H); 2.36 (broad d, J = 12 Hz : 1H); from 2.40 to 2.60 (mt : 3H); from 2.70 to 2.85 (mt : 2H); 2.91 (t, J = 7 Hz : 2H); from 3.00 to 3.30 (mt : 2H); 3.57 (s : 3H); 3.89
35 (s : 3H); 7.05 (dd, J = 6 and 3.5 Hz : 1H); 7.18 (dd, J = 3.5 and 1 Hz : 1H); 7.49 (dd, J = 9 and 3 Hz : 1H); 7.61 (dd, J = 6 and 1 Hz : 1H); 7.73 (d, J = 3 Hz : 1H); 7.92 (d, J = 5 Hz : 1H); 8.03 (d, J = 9 Hz : 1H); 8.90 (d, J = 5 Hz : 1H).

The methyl (3R,4R)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]piperidine-3-carboxylate may be obtained using the method described in patent application
5 FR 99 11679.

Example 5

(3R,4R)-4-[3-Oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-
10 (2,3,5-trifluorophenyl)prop-2-ynyl]piperidine-3-carboxylic
acid

A solution of 1 g of methyl (3R,4R)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(2,3,5-trifluoro-
15 phenyl)prop-2-ynyl]piperidine-3-carboxylate in 10 cm³ of a 5N aqueous hydrochloric acid solution is stirred for 4 hours at a temperature in the region of 80°C. After cooling to a temperature in the region of 20°C, 10 cm³ of water, then 10 cm³ of chloroform, and then
20 1.9 g of powdered sodium hydrogen carbonate are added. The mixture is extracted with 3 times 10 cm³ of chloroform. The organic phases are pooled, dried over sodium sulfate, filtered, and then concentrated under reduced pressure (5 kPa) at a temperature in the region
25 of 40°C. The residue obtained is purified by chromatography under a nitrogen pressure of 50 kPa, on a column of silica gel (particle size 20-45 µ; diameter 2.5 cm; 30 g), eluting with a mixture of dichloromethane-methanol (96/4 by volume) and
30 collecting first a fraction of 150 cm³, and then fractions of 10 cm³. Fractions 5 to 22 are pooled, and then concentrated as above. 0.583 g of (3R,4R)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(2,3,5-trifluorophenyl)prop-2-ynyl]piperidine-3-carboxylic
35 acid, in the form of a green-colored solid which melts at around 70°C, is obtained.

¹H NMR spectrum (300 MHz, (CD₃)₂SO d₆, δ in ppm): from 1.60 to 1.95 (mt : 5H); 2.44 (mt : 1H); 2.58 (broad d,

J = 11 Hz : 1H); 2.73 (mt : 2H); 2.92 (mt : 1H); 3.19 (mt : 2H); 3.67 (s : 2H); 3.88 (s : 3H); 7.32 (mt : 1H); 7.48 (dd, J = 9 and 2.5 Hz : 1H); 7.63 (mt : 1H); 7.72 (d, J = 2.5 Hz : 1H); 7.92 (d, J = 4.5 Hz : 1H);
5 8.02 (d, J = 9 Hz : 1H); 8.89 (d, J = 4.5 Hz : 1H); from 12.30 to 12.80 (broad unresolved peak : 1H).
Optical rotation: $\alpha_D^{20} = +27.9^\circ \pm 0.8$, in 0.5% methanol.

10 Methyl (3R,4R)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(2,3,5-trifluorophenyl)prop-2-ynyl]piperidine-3-carboxylate

A mixture of 17.28 g of methyl (3R,4R)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-(prop-2-ynyl)-
15 piperidine-3-carboxylate in 173 cm³ of triethylamine is stirred for 5 minutes under an inert atmosphere at a temperature in the region of 20°C. 4.05 g of tetrakis(triphenylphosphine)palladium, 0.834 g of
20 cuprous iodide and 7.9 g of 1-bromo-2,3,5-trifluorobenzene are added. The mixture is stirred for 2 hours at a temperature in the region of 80°C. After cooling to approximately 20°C, 150 cm³ of ethyl acetate and 150 cm³ of water are added to the reaction mixture,
25 which is then separated after settling out. The aqueous phase is extracted with 3 times 150 cm³ of ethyl acetate. The organic phases are pooled, washed with 5 times 150 cm³ of water, dried over sodium sulfate, filtered, and concentrated under reduced pressure
30 (5 kPa) at a temperature in the region of 40°C. The residue obtained is purified by chromatography under a nitrogen pressure of 50 kPa, on a column of silica gel (particle size 20-45 μ ; diameter 7 cm; 600 g), eluting with pure ethyl acetate and collecting first a fraction
35 of 2.5 l, and then fractions of 250 cm³. Fractions 2 to 29 are pooled and then concentrated as above. 18.4 g of methyl (3R,4R)-4-[3-oxo-3-(6-methoxyquinolin-4-yl)propyl]-1-[3-(2,3,5-trifluorophenyl)prop-2-ynyl]-piperidine-3-carboxylate, in the form of a yellow oil,

are obtained.

¹H NMR spectrum (400 MHz, (CD₃)₂SO d₆, δ in ppm): from
1.55 to 1.95 (mt : 5H); 2.39 (mt : 1H); 2.58 (broad d,
5 J = 10 Hz : 1H); 2.68 (mt : 1H); 2.82 (mt : 1H); 2.91
(mt : 1H); 3.09 (mt : 1H); 3.23 (mt : 1H); 3.58 (s :
3H); 3.61 (s : 2H); 3.88 (s : 3H); 7.31 (mt : 1H); 7.49
(dd, J = 9 and 2.5 Hz : 1H); from 7.55 to 7.65 (mt :
1H); 7.73 (d, J = 2.5 Hz : 1H); 7.92 (d, J = 4.5 Hz :
10 1H); 8.02 (d, J = 9 Hz : 1H); 8.89 (d, J = 4.5 Hz :
1H).